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Primary Thrombocythemia and Pregnancy: Treatment and Outcome in Fifteen Cases

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Pregnancy in patients with primary thrombocythemia (PT) is reported to be often complicated by recurrent abortion and fetal growth retardation. Fifteen pregnancies in nine patients with PT are reported. Nine pregnancies had a good outcome, with the birth of a healthy infant. There were two spontaneous abortions and three intrauterine deaths. One pregnancy was electively terminated after extensive thrombosis in the splanchnic district requiring surgical entero-resection. In five pregnancies the mother received no treatment; in ten pregnancies acetylsalicylic acid (ASA) was prescribed to the mother as soon as she was found pregnant, subcutaneous heparin was added from the middle trimester in seven cases. In patients treated with ASA and subcutaneous heparin pregnancies had a good outcome. Administration of ASA and heparin during pregnancy appears to improve the outcome in patients with PT and can prevent severe maternal complications, but requires close monitoring. © 1996 Wiley-Liss, Inc.

Key words: primary thrombocythemia, pregnancy, treatment, outcome

INTRODUCTION

Primary thrombocythemia (PT) is an infrequent clonal myeloproliferative disorder [1,2] characterised by persistent elevation of platelet count. Typical complications are hemorrhage and thrombosis [3] related to the abnormal platelet number, morphology, and function [4].

The age distribution of the disease has two peaks, one in the upper middle age with males and females equally affected and one earlier in life, mainly affecting women [5]. It is still controversial whether acetylsalicylic acid (ASA) lowers the incidence of vaso-occlusive complications in young patients [6–8].

Pregnancy in women with PT can be complicated by recurrent abortion and fetal growth retardation [9–11] and the number of reported cases is increasing [12–18]. ASA has been recommended to prevent abortions and intrauterine fetal deaths resulting from thrombotic events in the placenta, but its efficacy has not been assessed in many cases [19].

We report here the outcome of fifteen pregnancies in nine patients with PT, the antiplatelet and anticoagulant treatment received and the complications that arose.

MATERIALS AND METHODS

Patients

All patients fulfilled the diagnostic criteria of the Polycythaemia Vera Study Group [20]. Hematological findings at diagnosis are shown in Table I. Patient 5 had had splenectomy for infarction in splenomegaly 4 years earlier and had suffered a thrombosis of the supra-hepatic veins (Budd-Chiari syndrome) 2 years before PT was diagnosed. Patients 7 and 8 had had transient ischemic attacks (TIA) before becoming pregnant. All others were asymptomatic. All patients were negative for lupus-like anticoagulant and anticardiolipin antibodies.

Pregnancy Outcome

Table II shows the outcome of the first eight pregnancies in seven of the nine patients; Table III lists the other seven

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TABLE I. Hematological Findings at Diagnosis in Nine Patients With Primary Thrombocythemia in Pregnancy

Patient	Age (years)	Platelets ($\times 10^9$/L)	Hemoglobin (g/L)	White cell count ($\times 10^3/\mu$L)
1	26	650	136	5.5
2	30	850	147	7.5
3	22	800	134	7.3
4	30	930	148	8.3
5	34	1,600	128	14.0
6	27	900	126	9.3
7	19	700	129	6.3
8	26	920	140	9.5
9	23	960	123	7.5

TABLE II. Outcomes of Eight Pregnancies in Seven Patients With Primary Thrombocythemia*

Patient	Pregnancy	Antenatal complications	Treatment in pregnancy	Outcome	Fetus or newborn	Histology of placenta	Post-natal complications
1	I	Nil	Nil	5 weeks EA	—	—	Budd-Chiari
2	I	Nil	Nil	27 weeks IUFD	270 g	—	Budd-Chiari
4	I	Nil	Nil	8 weeks SA	—	—	Nil
5	I	Budd-Chiari, Splenectomy	ASA	37 weeks CS	2,200 g	Multiple infarction	Nil
6	I	Nil	Nil	7 weeks SA	—	—	Hemorrhage
7	I	Nil	ASA	40 weeks ND	3,440 g	—	TIA
8	I	Nil	Nil	28 weeks IUFD	700 g	Multiple infarction	Nil
	II	Nil	ASA	28 weeks IUFD	650 g	Multiple infarction	TIA

*EA = elective abortion; IUFD = intrauterine foetal death; SA = spontaneous abortion; CS = Cesarean section; ND = normal delivery; TIA = transient ischemic attack.

TABLE III. Outcomes of Seven Pregnancies in Seven Patients With Primary Thrombocythemia, Requiring Cesarean Section

Patient	Pregnancy	Antenatal complications	Treatment in pregnancy	Outcome	Newborn	Histology of placenta	Post-natal complications
3	II	Nil	ASA-Heparin	39 weeks	3,060 g	Inflammation of villi	Nil
4	II	Nil	ASA-Heparin	37 weeks	2,950 g	Fibrinoid necrosis	Nil
5	II	Budd-Chiari	ASA-Heparin	39 weeks	2,460 g	Fibrinoid necrosis	Nil
6	II	Nil	ASA-Heparin-ATIII	34 weeks	2,200 g	Fibrinoid necrosis	Nil
7	II	TIA	ASA-Heparin	38 weeks	2,900 g	Multiple infarction	Nil
8	III	TIA	ASA-Heparin	38 weeks	3,250 g	—	Nil
9	I	Nil	ASA-Heparin-ATIII	32 weeks	1,950 g	Multiple infarction	Nil

pregnancies in seven of the nine patients. Altogether nine pregnancies reached a gestational week compatible with fetal survival. One resulted in the delivery of a healthy infant at term. Eight required Cesarean sections between weeks 32 and 39, with delivery of eight healthy newborns. The obstetrician reported fetal distress demonstrated by cardiotocography and reduced placental perfusion evaluated by Doppler echography of the umbilical arteria.

Two of these babies were small for gestational age. The placenta was examined histologically in seven of the eight cases, and in six had multiple infarctions.

Patient 1 had multifocal thrombosis involving the superior mesenteric, portal and splenic vein at 5 weeks of gestation; the extent of ischemic necrosis of the small bowel required extensive surgical entero-resection and the pregnancy was electively terminated. Patients 4 and 6 suffered spontaneous abortions at 8 and 7 weeks of pregnancy. Abortion in patient 6 was complicated by heavy bleeding, possibly due to the retained products of conception, because the patient did not suffer excessive blood loss in her second pregnancy despite the use of ASA and heparin.

Three pregnancies resulted in intrauterine fetal death, all occurring between the 27th and 28th week of gestation.

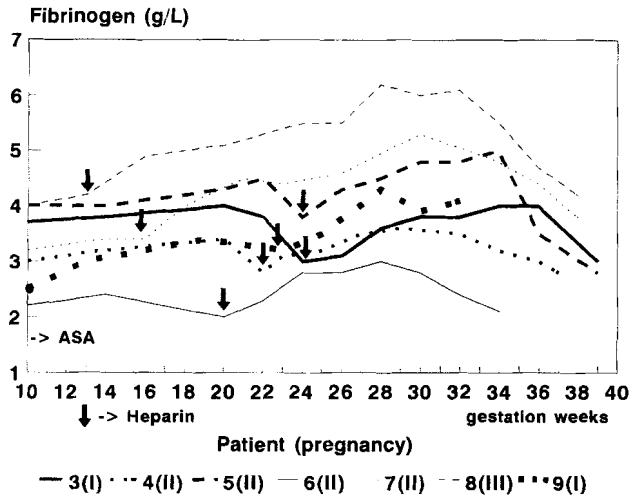

Fig. 1. Changes in fibrinogen in seven pregnancies. Arrows mark the start of subcutaneous heparin therapy.

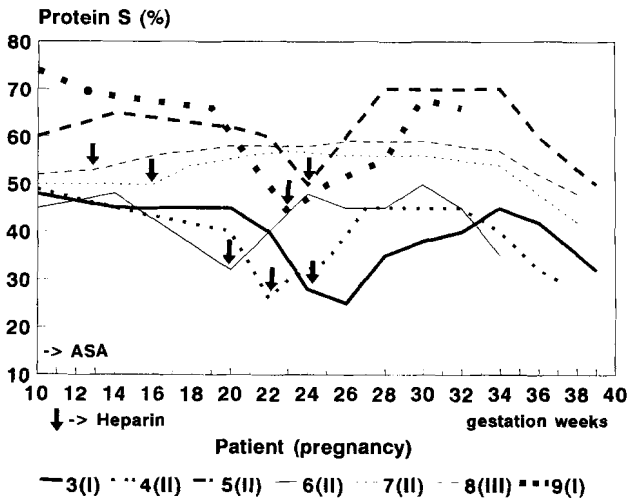

Fig. 2. Changes in protein S in seven pregnancies. Arrows mark the start of subcutaneous heparin therapy.

Placental histology, available in two cases, showed multiple infarctions.

Treatment

No anti-platelet treatment was given in five pregnancies; oral ASA was given at a 50 mg dose every day in three pregnancies from the 5th week onwards (Table II). In seven patients subcutaneous heparin 5,000 IU every 8 hr was added to ASA during their pregnancy (Table III). This additional treatment was started when the fibrinogen concentration pattern no longer showed the physiological continuous increase in pregnancy or when the protein S activity fell below 35%. The normal range of protein S activity in pregnancy is from 40 to 60% [21]. Changes in fibrinogen and protein S levels and the beginning of heparin therapy are documented in Figures 1 and 2. We always measured fibrinogen levels in our laboratory with the same equipment, using a prothrombin-derived method. All patients were also monitored for hemocytometry, prothrombin time, partial thromboplastin time, protein C, and antithrombin III.

In patient 6, at her second pregnancy, receiving ASA and subcutaneous heparin, antithrombin III 3,000 IU i.v. was given after the Cesarean section because antithrombin III activity had dropped to 40%. In patient 9, receiving ASA and subcutaneous heparin, antithrombin III 2,000 IU i.v. was added every other day beginning from the 27th week, to keep antithrombin III activity above 80%.

This was a non-randomised, retrospective study.

RESULTS

Table IV summarizes the outcome of pregnancies treated with the association of ASA administered as soon as possible and heparin beginning from the second trimester, compared to untreated previous pregnancies or those treated only with ASA. Because of the small number of cases, we applied Fisher's exact test, which showed a significant difference between the outcome for patients treated with ASA and heparin and previous pregnancies.

TABLE IV. Two-by-Two Contingency Table Analyses*

	Treated with ASA and heparin (7)	Untreated or only with ASA (8)
Live birth (9)	7	2
Abortion or fetal loss (6)	0	6

*Fisher's exact test: $P < 0.01$.

DISCUSSION

The treatment of PT differs according to the patient's age and whether there are complications in the medical history [18,22]. In asymptomatic patients below 40 years of age chemotherapy is not recommended; Interferon is preferable and has also been used successfully in pregnancy [17,23,24]. Generally the therapeutic control of myeloproliferative disorder in pregnancy is not necessary. Platelet-pheresis can be used for a short period in acute situations but has a limited part [14].

Thrombotic complications of PT are reported in pregnancy, with a high rate of fetal morbidity and mortality [5,7,9–11,13,14] and in most cases placentas show multiple infarctions.

Normal pregnancy is characterised by a progressive increase in clotting activation, as demonstrated by signs of increased thrombin generation and fibrin deposition

[25]. This clotting activation is not accompanied by evidence of platelet activation and this platelet hyporesponsiveness is a unique feature of pregnancy and the feto-neonatal period [26]; it is due to increased vascular production of prostacyclin (PGI_2), the most potent endogenous inhibitor of platelet aggregation. Impairment of this compensatory mechanism is associated with pre-eclampsia and intrauterine growth retardation. During pregnancy in PT patients, PGI_2 production may be insufficient for the augmented platelet mass, resulting in decreased antiaggregant effectiveness.

Treatment with ASA has been shown to have beneficial effects in reducing pre-eclampsia and intrauterine growth retardation in high-risk patients [27]. In pregnant women low-dose ASA selectively suppresses maternal platelet thromboxane B2 while sparing vascular prostacyclin [28], and one of the aims of prophylactic use of ASA is to allow complete trophoblastic invasion of the spiral arteries. As this process takes place before 20 weeks of gestation, the ASA treatment must be started as soon as possible during gestation, preferably early in the second trimester. In a large randomised trial the use of low-dose ASA alone for the prevention of pre-eclampsia significantly reduced the likelihood of preterm delivery, but the reduction of proteinuric pre-eclampsia was not significant, nor was there any significant effect on the incidence of intrauterine growth retardation or of stillbirth and neonatal death [29].

In normal pregnancies there is a progressive reduction in the platelet count, which at term averages 15–20% of the count after few weeks of pregnancy. This is compatible with plasma volume expansion. In patients with PT a marked drop to nearly normal values can be observed close to term [30], and platelets return rapidly to the pre-pregnancy level within several days of delivery. The mechanism of this normalization during untreated pregnancy in thrombocythemia is not known, though it may be due to a progressive increase in platelet consumption during pregnancy and close to term.

Inadequate control of platelet activation causes increased platelet consumption and enhancement of clotting activation with pathological fibrin deposition. This excessive generation of thrombin is responsible for the reduction of fibrinogen and natural anticoagulants like antithrombin III and protein S observed in our patients. Subcutaneous heparin is an effective means of restoring the physiological clotting activation and may have a place in prophylaxis of the enhanced coagulation status of late pregnancy and puerperium [31], also in other clinical states in which the platelets are chiefly involved, like antiphospholipid syndrome [32]. All patients treated with subcutaneous heparin in the last trimester and in the early puerperium had a live birth and none had complications, with no bleeding problems during pregnancy or in postpartum.

CONCLUSIONS

In our experience pregnancy is not contraindicated in patients with asymptomatic PT. Normal pregnancy and delivery are possible in untreated patients too, as recently reported [33,34], but close monitoring of the mother and fetus is necessary. In some cases the use of ASA and heparin should be used to reach a gestational age compatible with fetal survival and to avoid maternal complications, but this conclusion needs to be confirmed by prospective randomized trials or meta-analyses.

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